UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/320,585	12/01/2011	Dongan Wang	055514/412509	9090

826 7590 04/24/2017

ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER
MARTIN, PAUL C

ART UNIT	PAPER NUMBER
1653	

NOTIFICATION DATE	DELIVERY MODE
04/24/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomail@alston.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DONGAN WANG, KAI SU,
YIHONG GONG, and TING TING LAU

Appeal 2016-002682
Application 13/320,585
Technology Center 1600

Before DONALD E. ADAMS, JEFFREY N. FREDMAN, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1] under 35 U.S.C. § 134 involving claims to compositions. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

"Tissue engineering techniques generally require the use of a temporary scaffold as a three-dimensional template for initial cell attachment and subsequent tissue formation. The ability of the scaffold to be metabolised by the body allows it to be gradually replaced by new cells to

---

[1] Appellants identify the Real Party in Interest as Nanyang Technological University (*see* App. Br. 2).

form functional tissue" (Spec. ¶ 3). "The invention is based on the finding that cavities can be formed in a hydrogel matrix using degradable and surface cross-linked particles that degrade at a faster rate compared to the hydrogel matrix at a given condition" (Spec. ¶ 46).

The Claims

Claims 1–6 and 8–26 are on appeal. Claim 1 is representative and reads as follows (underlining omitted):

> 1. A composition comprising one or more species of living cells, and a mixture of at least one degradable hydrogel and at least one kind of degradable and surface cross-linked particle, wherein the at least one kind of degradable and surface cross-linked particle comprises a material which degrades faster than the at least one degradable hydrogel at a given condition, wherein the at least one kind of degradable and surface cross-linked particle has a surface comprising additional reactive groups to bind the one or more species of living cells to its surface such that it forms a degradable particle comprising a living cell, and wherein one or more degradable particle comprising a living cell are comprised in the at least one degradable hydrogel, and wherein the at least one degradable hydrogel of the mixture is formable to a hydrogel matrix comprising cavities formable by the faster degrading surface cross-linked particle.

The issues

The Examiner rejected claims 1–6 and 8–26 under 35 U.S.C. § 103(a) as obvious over Tan,[2] Risbud,[3] Reginato,[4] and Cosmobio[5] (Final Act. 3–7).

The Examiner finds Tan teaches "PLGA/gelatin-RGDS microspheres are potentially applicable as cell carriers, which may be further piled into a 3-D scaffold" (Ans. 4). The Examiner finds Risbud teaches "natural polymeric gels such as hyaluronic acid, collagen, *alginate* and *chitosan* have been used successfully for immobilization and maintain the differentiated phenotype of *chondrocytes*" (Ans. 5). The Examiner finds Risbud teaches "fiber scaffolds or other porous structures are used to achieve initial biomechanical stability suitable synthetic biodegradable poly(a-hydroxyesters) such as *polylactic acid, polyglycolic acid* and copolymer PLGA" (*id.*).

The Examiner finds it inherent that "PLGA/gelatin microspheres would degrade faster than the degradable hydrogel at a given condition, as this appears to be a characteristic of the PLGA/microspheres" (Ans. 6).

---

[2] Tan et al., *RGD Modified PLGA/Gelatin Microspheres as Microcarriers for Chondrocyte Delivery*, 91B J. BIOMED. MATER. RES. PART B: APPL. BIOMATER. 228–238 (2009) ("Tan").
[3] Risbud et al., *Tissue engineering: advances in in vitro cartilage generation*, 20 TRENDS IN BIOTECHNOLOGY 351–356 (2002) ("Risbud").
[4] Reginato et al., *Formation Of Nodular Structures Resembling Mature Articular Cartilage In Long-Term Primary Cultures Of Human Fetal Epiphyseal Chondrocytes On A Hydrogel Substrate*, 37 ARTHRITIS & RHEUMATISM 13381349 (1994) ("Reginato").
[5] Cosmobio, http://www.cosmobio.co.jp/export_ e/products/detail/alginate.asp?entry_id= 12589 (Accessed Sept. 12, 2014).

The Examiner finds the combination of Tan and Risbud obvious because "a combined composition of degradable PLGA/gelatin microspheres and degradable hydrogel would have the characteristics of sufficient exchange of nutrients and wastes as well as a tissue engineering platform suitable for the transplantation of cells characterized by 3-D immobilization and maintaining the differentiated phenotype of *chondrocytes*" (*id.*).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that claim 1 is obvious over Tan, Risbud, and Reginato?

Findings of Fact

1. Tan teaches "PLGA/gelation microspheres were fabricated . . . EDAC was used to covalently immobilize RGDS peptides onto the PLGA/gelatin microspheres" (Tan 229, col. 2).

2. Tan teaches "after PBS . . . or DMEM . . . incubation, many micron pores emerged on the PLGA/gelatin . . . and PLGA/gelatin-RGDS . . . microspheres" (Tan 233, col. 2).

3. Tan teaches "to detect the chondrocyte viability as a function of culture time . . . The viability on the control PLGA, PLGA/gelatin, and PLGA/gelatin-RGDS microspheres increased 2, 2.3, and 2.4 times compared to 1 day after the cells were cultured for 7 day[s]" (Tan 234, col. 2).

4. Tan teaches "[c]ompared to that of the control PLGA microspheres, a significantly higher optical density ($p < 0.05$) which is proportional to cell viability, was recorded on the PLGA/gelatin and PLGA/gelatin-RGDS microspheres after the cells were cultured for 3 day[s]" (Tan 234, col. 2).

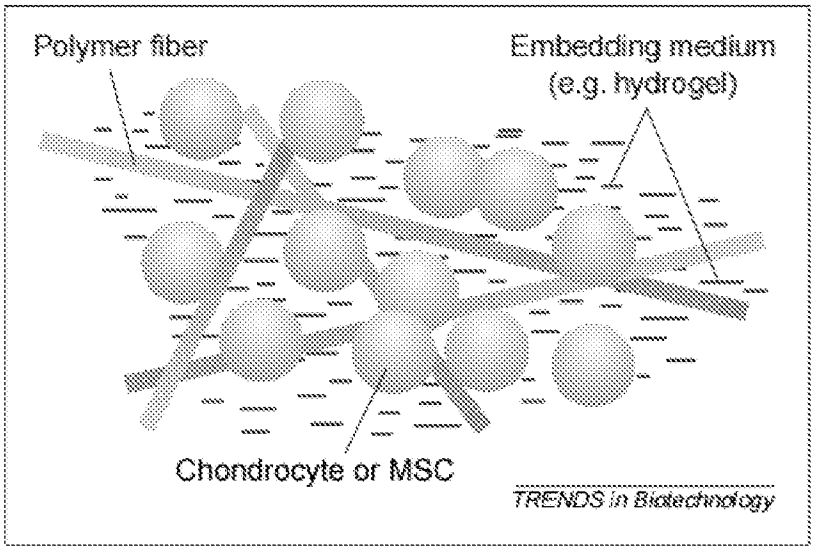
5. Tan teaches "the PLGA/gelatin-RGDS microspheres are potentially applicable as cell carriers, which may be further piled into a three-dimensional scaffold for in vivo chondrogenesis" (Tan 237, col. 1).

6. Risbud teaches:

> Specially designed biomaterial scaffolds are one of the key components in tissue engineering. Research is focused on developing bioresorbable scaffolds that exhibit optimal physical properties coupled with excellent biocompatibility. Scaffolds act as shape and guidance templates for *in vitro* and *in vivo* tissue development. For cartilage and bone tissues, a suitable scaffold provides initial mechanical stability and supports even cell distribution. Natural polymeric gels, such as hyaluronic acid, collagen, alginate and chitosan, have been used successfully. These scaffolds permit 3D immobilization of cells and maintain the differentiated phenotype of chondrocytes.

(Risbud 352, col. 2; citations omitted).

7. Figure 3 of Risbud is reproduced below:



"**Fig. 3**. Schematic drawing showing the strategy of developing tissue engineered cartilage constructs using fibres and embedding substances.

Embedding substances offer 3D immobilization and uniform distribution of cells in the fibre mesh" (Risbud 353, col. 2).

8. Risbud teaches "solid bio-resorbable fibre scaffolds or other porous structures are used to achieve initial biomechanical stability. Synthetic biodegradable poly(α-hydroxy esters) such as polylactic acid (PLLA), polyglycolic acid (PGA) and copolymer PLGA have been used extensively in this context" (Risbud 352, col. 2 to 353, col. 1).

9. Risbud teaches: "Injectable in situ crosslinkable polymeric preparations that entrap cells have been designed and techniques that combine the advantages of both porous fibre structures and gels are being explored as suitable alternatives to either gels or fibre scaffolds" (Risbud 353, col. 1).

10. Reginato teaches chondrocytes "were cultured for up to 180 days on plastic dishes previously coated with the hydrogel, poly-(2-hydroxyethyl methacrylate)" (Reginato 1338, abstract).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

Analysis

We adopt the Examiner's findings regarding the scope and content of the prior art (Final Act. 3–7; FF 1–10) and agree that the claimed

composition would have been obvious over the teachings of Tan, Risbud, and Reginato.[6] We address Appellants' arguments below.

Appellants contend: "In the context of Tan, where the PLGA/gelatin-RGDS microspheres are consistently referred to as being capable of forming scaffolds, it can be seen that the microspheres and the cells are the components that are envisaged for forming a three-dimensional scaffold on their own with no other components" (App. Br. 5).

We do not find this argument persuasive. "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). A reference "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *Id.*

Here, Risbud teaches an engineered tissue composed of living chondrocyte cells, a degradable hydrogel, and a degradable polymer (FF 7). Risbud teaches the hydrogel may be composed of alginate and chitosan (FF 6; *cf.* Spec. 14:28) and the degradable polymer may be composed of PLGA (FF 8).

While Risbud does not teach the PLGA polymer is in particle form or comprises a binding reactive group, Tan teaches PLGA microspheres with the binding reactive group of RGDS peptides (FF 1). Tan teaches the PLGA microspheres are degradable (FF 2) and increase cell viability (FF 3–4). Tan

---

[6] We need not rely upon CosmoBio for any limitation of claim 1. The Board may rely on fewer than all of the references relied on by the Examiner in an obviousness rationale without designating it as a new ground of rejection. *In re Bush*, 296 F.2d 491, 496 (CCPA 1961).

further teaches "the PLGA/gelatin-RGDS microspheres are potentially applicable as cell carriers, which may be further piled into a three-dimensional scaffold for in vivo chondrogenesis" (FF 5).

We therefore agree with the Examiner's obviousness position that the ordinary artisan, interested in forming engineered tissue composed of cells, hydrogel, and polymer cell carriers such as PLGA as disclosed by Risbud, would have utilized Tan's PLGA/gelatin-RGDS microspheres as cell carriers for improved cell viability (FF 4) in the hydrogel matrix of Risbud (FF 7) (*see* Ans. 5).

Appellants contend "Tan clearly distinguishes porous or hydrogel scaffolds from microspheres and provides that porous scaffolds produce less cell proliferation than cells cultured on microspheres" (App. Br. 6). Appellants contend:

> In view of these teachings of Tan against the use of porous or hydrogel scaffolds in conjunction with the teachings of Tan regarding forming 3D scaffolds from microspheres, one of ordinary skill in the art would not find it obvious to use a hydrogel formable to a hydrogel matrix comprising cavities formable by the faster degrading surface cross-linked particle.

(*id.*).

We find the teaching away arguments unpersuasive. A teaching away requires a reference to actually criticize, discredit, or otherwise discourage the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) ("The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed").

Here, Tan recites microspheres and porous hydrogel scaffolds as alternatives, where "cell culture on the microspheres may produce a larger number of cells" (Tan 228, col. 2). However, Tan never specifically teaches that hydrogel scaffolds are undesirable or will not work, only that microspheres are a desirable approach (FF 5). Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments. *In re Susi*, 440 F.2d 442, 446 n.3 (CCPA 1971).

Appellants contend "in the unlikely event the microspheres of Tan were combined with the hydrogel matrices of Risbud, this combination fails to establish the subject matter of the present claims. The combination would only result in the microspheres being grown on the surface of one of the preformed hydrogel matrices and not in the preformed hydrogel matrices" (App. Br. 8).

We do not find this argument persuasive because Risbud clearly demonstrates embedding the polymers, such as PLGA, within the three dimensional hydrogel medium (FF 7). Indeed, Risbud suggests such a combination, teaching "polymeric preparations that entrap cells have been designed and techniques that combine the advantages of both porous fibre structures and gels are being explored as suitable alternatives to either gels or fibre scaffolds" (FF 8). The ordinary artisan would find it obvious that the microspheres would therefore be "in" the hydrogel, as required by claim 1 (*see* FF 7).

Appellant contends "the contemplated modification would still fail to render obvious the recited composition where at least one degradable

hydrogel of the mixture is formable to a hydrogel matrix comprising cavities formable by the faster degrading surface cross-linked particle" (App. Br. 9).

We find this argument unpersuasive because the engineered tissue rendered obvious by Risbud and Tan, comprising chondrocytes growing PLGA-gelatin RGDS microspheres embedded in a hydrogel matrix (FF 1–8), would inherently result in degradation of the PLGA microspheres to form pores as shown by Tan (FF 2). We therefore agree with the Examiner that "as the composition of the combined prior art comprises the same components as claimed, it is inherent in the prior art that the composition would comprise a hydrogel matrix comprising cavities formable by the faster degrading surface cross-linked particle" (Ans. 10).

Conclusion of Law

The evidence of record supports the Examiner's conclusion that claim 1 is obvious over Tan, Risbud, and Reginato.

SUMMARY

In summary, we affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over Tan, Risbud, and Reginato. Claims 2–6 and 8–26 fall with claim 1.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED